21. FUTURE STUDIES OF CONGENITAL MALFORMATIONS IN DIFFERENT COUNTRIES

TYPES OF STUDIES NEEDED

The levels of perinatal mortality and later infant losses fall in all countries as medical care and socio-economic conditions improve, and an increasing proportion of the remaining wastage is that predetermined at birth, either by the genotype of the foetus or by ill-understood environmental influences acting in the uterus in the first 10 weeks of pregnancy before major organogenesis is complete. There seems to be no possibility in the foreseeable future of prevention of these defects where the main cause is the situation either at one or at many gene loci or in abnormalities of chromosomal number or structure, i.e., the defects are in the hereditary material. The factors determining most of recurring gene or chromosomal mutations are unknown. However we explain maintenance of the frequencies of genes contributing to any multigenic explanations, we cannot define the genotypes concerned.

That the maintenance of part of this variability in populations is essential in order to enable populations and individuals to adapt to different and to changing environments is axiomatic in our current understanding of the genetical structure of populations. The corollary to this is that many of the developmental deviations are the price which the individual and the population have to pay for the benefits of the successful adaptation of the human species. It would appear, therefore, that the first objectives of preventive medicine in this field must be to try to identify and then control the environmental factors. It follows that epidemiological studies should be orientated to this end and that they should have as their broad objectives the separation out as far as possible of defects mainly determined by the foetal genotype and those where the genetic contribution, if any, is unimportant relative to the environmental influences. The next step would logically be to try to identify the harmful environmental components. It would be out of place here to speculate in detail as to the types of study which might be undertaken with these objectives in view but they must surely include investigations of maternal health in pregnancy relative to the conditions of the children who are the outcome of these pregnancies, studies of the genetic factors which disturb pregnancies, and attempts to separate ethnic geographic and socio-economic effects. They must also include attempts to relate the events in the first few weeks of pregnancy to the outcome, embracing study of all the factors already incriminated, including certain drugs, diet, radiation and so on. Such studies are inevitably extensive and very tedious and time-consuming. Most of them would have to be orientated to the investigation of individual malformations because there can be little doubt that etiological factors are relatively, if not entirely, specific. It follows that such studies must be associated with clinical and clinical-pathological investigations designed to reduce to a minimum heterogeneity within groups of cases at present regarded as homogeneous because of their clinical similarity.

PARTICULARLY FAVOURABLE OPPORTUNITIES IN CERTAIN HOSPITALS FOR STUDIES OF SOME SPECIFIC PROBLEMS

In the course of studying this very large amount of data, it became clear that there were some hospitals where there were unique opportunities for looking at particular problems concerning congenital malformations. In some, for example, there were sufficient numbers of people of different ethnic origins admitted to the hospital to enable large amounts of information to be collected over a few years. In others, the numbers of births per year alone offered the opportunity of testing over a relatively short time various hypotheses by *ad hoc* collection of data. In others again, the very high frequency of parental consanguinity could be exploited in many ways which would illuminate a facet of the nature-nurture controversy. No doubt every hospital has some unique situation which could be exploited. It is inconceivable that there would not be a mine of valuable information to be exploited even from the past records of any really large maternity hospital which had an up-to-date and efficient records system, and where the staff were sufficiently interested to set down accurately what was to be recorded.

It is invidious to select, but from the data it would appear that special opportunities are exemplified by the situations in Alexandria, Bombay, Mexico City and Singapore.

Alexandria

In the Shatby hospital there are about 5000 births per annum, and it is understood that another large hospital in Alexandria will shortly be in closer relationship with the Shatby. Associated with the hospital is a midwifery service providing attendance at home confinements. Over 30% of all the women admitted to confinement in the hospital were related to their husbands and in 22% the relationship was that of first cousins. There is a very high rate of neural tube defects and a high dizygous twinning rate.

It may be surmised that a properly planned study would illuminate the relationships of consanguinity, neural tube defects, hydramnios, toxaemia and dizygous twinning. Such a study might well include collection of data on past pregnancies of mothers (which it was not possible to do in the present study) and investigation of the reproductive performances of sisters (including pairs who had, and who had not, married relatives). It might be possible, perhaps in conjunction with the Institute of Public Health, to undertake a study in Alexandria of hospital and home confinements in a relatively well-defined population in which the socio-economic status of parents had been classified and the consanguinity relationships worked out in considerable detail. Alternatively, sampling of non-hospital births in the city might serve the same purpose.

Bombay

In Bombay there is also a high consanguinity rate (about 10%), a high rate of neural tube defects and a relatively high dizygous twinning rate so that the problems are similar to those in Alexandria. In addition, mothers from many intra-marrying groups or castes are admitted to the hospital and over time information could be collected about the relative frequencies of malformations. There are considerable numbers of uncle-niece marriages in some of these groups, and these are of particular biological interest.

Mexico City

There are two very large maternity hospitals administered by the Ministry of Social Security in Mexico City, and together they represent some 50 000 births per year. The frequency of consanguinity is low, but as the numbers of births are so large, valuable information relative to the associations of mortality and malformation in a low consanguinity frequency population could be collected relatively rapidly. There appear to be many mothers with maternal diabetes admitted to these hospitals, and this situation is favourable to investigation of the difficult question whether malformations associated with diabetes in the mother are predominantly associated with those cases where the pregnancy was also complicated by hydramnios.

Finally, there is some evidence to suggest that in Mexico City the proportion of all pre-28th week losses that occurs between the 18th and 27th weeks is much higher than elsewhere. An analysis of the information collected on this point might serve to identify the characteristics of a high-risk group of mothers and give clues as to the etiology. The neural tube defect frequency in post-28th week births is rather high in Mexico City and it might be that there are also many with similar malformation in the pre-28th week group. Routine nuclear sexing of children in this group would also be of considerable interest.

Singapore

The Kandang Kerbau Hospital in Singapore has the distinction of appearing in " *Ripley* " and the *Guinness Book of Records* as the hospital where the largest number of infants in the world is born each year—namely, about 40 000. This represents about two-thirds of all the births in Singapore. In addition to this torrent of births, there are admitted each year some 3000 women for the treatment of abortions and another 3000 for gynaecological treatment.

The consanguinity recording in the present study in Singapore was of the simple type and might be expanded. The rate in the Chinese mothers, who preponderated, was low; however, it was high in Malay and Indian mothers. It will have been noted that the frequency of neural tube defects is low in Singapore although rather higher in Indian mothers, and a study within ethnic groups of the association of these defects with consanguinity would be of interest. The same applies to harelip and harelip and cleft palate, which have a high frequency in Singapore, so that sufficient cases could be accumulated to make worth while a serious attempt to resolve some of the heterogeneity which seems to be present in series of these cases. With such a large number of births occurring each day, a huge and valuable series of comparisons of nuclear sex and phenotypic sex at birth could be accumulated by the use of a simple buccal smear technique. It is fascinating to realize that every two days in that hospital we should expect a child with a sex chromosome anomaly to be born.

If any such studies could be undertaken in Singapore, they would be valuable; and it may be pointed out in passing, although it is perhaps not strictly relevant to this report, that the opportunities for study of early reproductive wastage, of hydatidiform mole and chorion-carcinoma, are quite unique. However, to take full advantage of these opportunities a prospective study using cytological, histological, biochemical and clinical techniques would be essential. Virtually nothing is known of any predisposition to mole determined by the maternal and foetal genotype and appropriate studies would be of great interest.

ACKNOWLEDGEMENTS

After living with a big study for five years, it seems strange but not unwelcome to reach this final stage. We have long looked forward to having the opportunity to thank many old friends and colleagues and new friends made in the course of this work.

It has been stressed repeatedly throughout this report that we have been acting as agents for our colleagues in all the co-operating centres, and it may seem odd also to include them in the acknowledgements, but we should like to emphasize how much we have enjoyed meeting them in the hospitals and to have had the pleasure of having a number of them in Oxford, some as passing visitors and four of them for various periods of time as attached workers. Only we, who have seen so many thousand returns, can realize how much work was put into this study in the various hospitals and with what care the record cards were completed. Many of the returns of malformations were accompanied by descriptive letters and we have sufficient photographs of congenital malformations to publish an atlas. From the Leonor Mendes de Barros Hospital in São Paulo, we received a photograph of each malformation reported and in many cases multiple photographs of *in vivo* and autopsy appearances.

Our thanks are also due to Dr Lowry Dobson and the late Dr Erwin Kohn, both of the World Health Organization, for their valuable advice, co-operation and enthusiasm, and to the Regional Offices of WHO for their advice and assistance.

In Oxford we are indebted to Professor Trueta and his colleagues for the number of technical translations from the Spanish, and to visiting workers who also helped with translations, notably Dr Z. Sestak from Zagreb, and Dr Salzano from Porto Alegre. Our colleague and staff member, Dr A. Barr, who is also a statistical advisor to the Oxford Regional Hospital Board, advised and helped with many statistical problems, and organized the punching and sorting of data for the basic tables in all centres. Only the constant interest and efficient help of Miss Smith, who is in charge of the machine room, made it possible to keep the work within schedule.

We are also grateful to other colleagues in the Unit for helpful discussion and suggestions. Miss K. Major and Miss R. Mason, the nurses in the Unit, carried out preliminary hand sorting of all the returned cards, separating out in each box any incomplete or miscoded cards and those referring to children who had died or were malformed. Mrs M. Parke carried out most of the numerical calculations and fortunately for us checked those which we had done ourselves. Finally, Mrs A. Naylor typed some of the tables reproduced by lithographs in the Basic Tabulations by Centres booklet, and Mrs E. L. Harris helped with much of the preliminary typing.

RÉSUMÉ

Cette étude collective sur les malformations congénitales a été entreprise à la suite d'une suggestion faite au cours d'une réunion tenue en 1959 à l'invitation de l'Organisation mondiale de la Santé. Un nombre relativement limité de renseignements ont été rassemblés au sujet des mères et des enfants, lors des naissances survenant après une grossesse d'au moins 28 semaines; les recherches ont été menées, sous les auspices de l'OMS, dans les centres dont la liste figure au début du rapport. Parmi les données recueillies figuraient l'âge et le groupe ethnique des mères, le nombre des grossesses antérieures, le degré de consanguinité des parents, la mention de naissance simple ou multiple, d'enfant mort-né, ou né vivant puis mort à l'hôpital, ou vivant à la sortie de l'hôpital. Chaque centre devait fournir en outre une description complète de la ou des malformations constatées chez un enfant. Certaines variations ont été observées dans le codage des informations relatives aux groupes ethniques et à la consanguinité, suivant les différents centres.

Le rapport exploite au total les données obtenues sur 416 695 naissances simples, 5022 naissances gémellaires, 63 naissances de triplés et 1 naissance de quadruplés, représentant au total l'aboutissement de 421 781 grossesses. Parmi les naissances simples, 5290 enfants présentaient des malformations (12,7 par 1000 naissances); la fréquence des malformations parmi les naissances multiples était du même ordre. La mortinatalité a été de 24,2 par 1000 naissances et la mortalité à l'hôpital de 16,0 par 1000 nouveau-nés vivants.

La section 2 présente les données relatives aux naissances simples, sous forme de tableaux, selon le sexe, les malformations et la survie et donne également leur répartition en fonction de l'âge maternel et de l'ordre de la grossesse.

Les sections suivantes, 3-17, exposent les aspects intéressants des données relatives aux enfants porteurs de malformations spécifiques ou de groupes de malformations. La section 18 discute les observations marquantes concernant les naissances multiples et la section 19 l'in-

fluence de la consanguinité sur la mortalité périnatale et les malformations.

L'examen des données fournit peu de renseignements intéressants au sujet du syndrome de Down (section 3) qui est probablement le plus fréquent des troubles graves du développement permettant la survie après la naissance; il en est de même pour les cardiopathies congénitales (section 6), les anomalies du diaphragme (section 8), le pied bot (section 10) et la luxation ou la subluxation congénitales de la hanche (section 11). La raison principale en est le manque d'uniformité des critères de diagnostic utilisés dans les différents hôpitaux.

On observe des différences réelles dans la fréquence des anomalies du système nerveux (section 4) suivant les populations. Ces états, très fréquents, provoquent environ la moitié de tous les décès imputables à l'ensemble des malformations congénitales. Il semble exister une corrélation significative entre la consanguinité des parents et la fréquence des différents types d'anomalies du système nerveux, en particulier à Alexandrie et à Bombay. Le rapport examine les différences d'atteinte de chaque sexe pour les différentes malformations. Ces lésions se développent pour la plupart au cours des premières semaines de la grossesse et leur fréquence très variable suivant le niveau socio-économique et la situation géographique à l'intérieur d'un même pays suggère une influence importante du milieu. L'étude des malformations du tube digestif (section 7) fait ressortir une fréquence plus grande des cas chez les garçons et l'hétérogénéité des anomalies trachéo-oesophagiennes et des malformations anales et uro-génitales associées.

Les malformations des membres et des extrémités (section 12) sont très diverses et d'interprétation difficile. On note au regard du faible nombre de cas de polydactylie cubitale une fréquence élevée du pouce bifide en Asie du Sud-Est. Les atteintes généralisées du squelette (section 13) se répartissent en deux groupes, l'un comprenant les syndromes dus à l'existence d'un gène spécifique unique, l'autre groupant des syndromes mal définis et d'étiologie inconnue. La section 14 qui traite des malformations uro-génitales est également hétérogène; dans la plupart des cas, l'identification de ces anomalies dépend de la mort ou de la survie de l'enfant et des résultats d'une éventuelle autopsie.

La section 15 analyse les malformations diverses que laisse subsister tout système de classification et dont certaines paraissent dues à un caractère génétique unique. Cette section examine toutes les données relatives aux anomalies de l'oreille, y compris l'atrésie du conduit auditif externe.

La section 16 traite des malformations multiples qui existent fréquemment chez un même enfant. Elle analyse sommairement les modalités de leur association et signale la fréquence particulière de certaines d'entre elles; on y souligne l'intérêt que présente l'exploitation de ce genre de données qui pourrait peut-être conduire à la mise au point de mesures préventives.

Les petites anomalies de faible importance ne sont pas mentionnées dans les tableaux récapitulatifs. Elles y auraient occupé une place importante, mais, de toute évidence, les différents centres les ont signalées avec plus ou moins de précision. La section 17 montre cependant l'importance numérique de malformations comme l'hypospadias, l'hydrocèle, la cryptorchidie, les hernies, les malformations mineures de l'oreille et les légères anomalies de la peau.

La section 18 envisage le cas des naissances multiples et évalue la fréquence des grossesses gémellaires à jumeaux monozygotes ou dizygotes. Les différences constatées selon les pays quant à la fréquence de la gémellité sont dues en majeure partie à un nombre plus élevé de jumeaux dizygotes. Les données recueillies vérifient approximativement la loi de Hellin. La mortalité périnatale et le nombre des malformations congénitales sont plus élevés chez les jumeaux monozygotes que chez les dizygotes. Une association remarquable a été observée: dans les différents centres, la fréquence des anomalies du système nerveux, en particulier de l'anencéphalie, est beaucoup moins élevée chez les jumeaux monozygotes que chez les jumeaux dizygotes.

La section 19 étudie les liens de consanguinité unissant à un degré variable les 14 000 parents d'enfants issus de grossesses simples. Les taux de consanguinité les plus élevés ont été observés à Alexandrie, Bombay et Kuala Lumpur. La mortalité à l'hôpital des enfants de parents consanguins (62,1 par 1000 naissances) a été considérablement plus élevée que celle des enfants de parents non consanguins (35,9 par 1000 naissances). Elle était particulièrement forte en cas de parenté étroite entre le père et la mère. Mais à Alexandrie, où les taux de consanguinité et de mortalité étaient très élevés, la mortalité a été la même parmi les enfants issus de parents consanguins que parmi les autres. Les relations entre consanguinité et malformations congénitales sont extrêmement complexes et de nombreuses théories génétiques cherchent à les expliquer. L'association le plus souvent rencontrée a été l'existence de malformations congénitales du système nerveux chez des enfants issus de parents consanguins, notamment à Alexandrie et à Bombay.

Les deux dernières sections du rapport (sections 20 et 21) contiennent un résumé des observations effectuées et des considérations sur la valeur de ces études. Elles rappellent l'objectif du présent travail, qui était de procéder à un premier examen des malformations congénitales pour mieux définir les problèmes et indiquer dans quelle direction il conviendrait d'orienter les recherches ultérieures.

REFERENCES

Barr, A. & Stevenson, A. C. (1961) *Ann. hum. Genet.*, **25**, 131-140

Böök, J. A. (1951) *Acta genet. (Basel)*, **2**, 289-311

Browne, D. (1955) *Arch. Dis. Childh.*, **30**, 42-45

Bulmer, M. G. (1960) *Ann. hum. Genet.*, **24**, 121-125

Butler, N. R. & Bonham, D. G. (1963) *Perinatal mortality. The first report of the 1958 British Perinatal Mortality Survey under the auspices of the National Birthday Trust Foundation*, Edinburgh & London, Livingstone

Carter, C. O. (1963) *Incidence and aetiology*. In: Norman, A. P., ed., *Congenital abnormalities in infancy*, Oxford, Blackwell, pp. 1-20

Carter, C. O. & Wilkinson, J. A. (1964) *Clin. Orthop.*, **33**, 119-128

Crow, J. F. (1958) *Hum. Biol.*, **30**, 1-13

Davison, B.C.C. (1965) *J. med. Genet.*, **2**, 233-242

Dobzhansky, T. (1955) *Cold Spr. Harb. Symp. quant. Biol.*, **20**, 1-15

Edwards, J. H. (1961) *Arch. Dis. Childh.*, **36**, 486-493

Fogh-Anderson, P. (1942) *Op. Domo Biol. hered. hum. Kbh.*, **4**, 1-266

Fraser, F. C. (1960) *Arch. Pediat.*, **77**, 151-154

Fraser, G. R. & Calnan, J. S. (1961) *Arch. Dis. Childh.*, **36**, 420-423

Fujino, H., Tanoka, K. & Yoshiharu, S. (1963) *Kyushu J. med. Sci.*, **14**, 317-331

Glancy, B. P. (1958) *Mongolism in Northern Ireland*, Belfast (MD thesis, Queen's University)

Guttmacher, A. F. (1953) *Obstet. and Gynec.*, **2**, 22-35

Hellin, D. (1895) *Die Ursache der Multiparität der unipaaren Tiere überhaupt und der Zwillingsschwangerschaft beim Menschen insbesondere*, München

Holder, T. M., Cloud, D. T., Lewis, J. E. & Pillings, G. P. (1964) *Pediatrics*, **34**, 542-549

Horne, H. W. (1957) *Fertil. and Steril.*, **9**, 67-69

International Commission on Radiation Protection (1966) *Hlth Phys.*, **12**, 239-302

Jeanneret, O. & MacMahon, B. (1962) *Amer. J. hum. Genet.*, **14**, 410-425

Josephson, J. E. & Waller, K. B. (1933) *Canad. med. Ass. J.*, **29**, 34-37

Kernahan, D. A. & Stark, R. B. (1958) *Plast. reconstr. Surg.*, **22**, 435-441

Komai, T. & Fukuoka, G. (1936) *Amer. J. phys. Anthrop.*, **21**, 433-447

Ladd, W. E. & Gross, R. E. (1934) *Amer. J. Surg.*, **23**, 167-183

Lejeune, J., Gautier, M. & Turpin, R. (1959) *C. R. Acad. Sci. (Paris)*, **248**, 1721-1722

Lerner, I. M. (1954) *Genetic homeostasis*, Edinburgh & London, Oliver & Boyd

Litt, S. & Strauss, H. A. (1935) *Amer. J. Obstet. Gynec.*, **30**, 728-730

McKenzie, J. & Craig, J. (1955) *Arch. Dis. Childh.*, **30**, 391-395

McKeown, T. & Record, R. G. (1960) *Malformations in a population observed for five years after birth*. In: *Ciba Foundation Symposium on Congenital Malformations*, London, Churchill, pp. 2-21

Mathieu, B. J., Goldowsky, S., Chaset, N. & Mathieu, P. L. (1953) *J. Pediat.*, **42**, 92-98

Millis, J. (1959) *Ann. hum. Genet.*, **23**, 171-174

Morton, N. E., Crow, J. F. & Muller, H. J. (1956) *Proc. nat. Acad. Sci. (Wash.)*, **42**, 855-863

Mudaliar, A. L. (1930) *J. Obstet. Gynaec. Brit. Emp.*, **37**, 753-768

Neel, J. V. (1958) *Amer. J. hum. Genet.*, **10**, 398-445

Neel, J. V. (1963) *Human population genetics, 1961*. In: *Proceedings of the Second International Congress of Human Genetics*, Rome, Istituto Mendel, vol. 1, pp. 31-36

Neel, J. V. & Schull, W. J. (1956) *The effect of exposure to the atomic bombs on pregnancy termination in Hiroshima and Nagasaki*, Washington, D.C., National Academy of Sciences (National Research Council, Publication No. 461)

Penrose, L. S. (1957) *J. ment. Defic. Res.*, **1**, 4-15

Penrose, L. S. (1963) *Biology of mental defect*, 3rd ed., London, Sedgwick & Jackson

Plessis, I. D. du (1944) *The Cape Malays*, Cape Town, Maskew Mitter Ltd.

Polman, A. (1951) *Genetica*, **25**, 29-78

Rank, B. K. & Thomson, J. A. (1960) *Med. J. Aust.*, **2**, 681-688

Schull, W. J. (1958) *Amer. J. hum. Genet.*, **10**, 294-343

Schull, W. J. & Neel, J. V. (1965) *The effects of inbreeding on Japanese children*, New York, Harper & Row

Searle, A. G. (1959) *Ann. hum. Genet.*, **23**, 279-288

Smårs, G. (1961) *Osteogenesis imperfecta in Sweden: clinical, genetic, epidemiological and socio-medical aspects*, Stockholm, Svenska Bokförlaget

Stevenson, A. C. (1957) *Amer. J. hum. Genet.*, **9**, 81-91

Stevenson, A. C. (1959) *Radiat. Res.*, Suppl. 1, pp. 306-325

Stevenson, A. C. & Warnock, H. A. (1959) *Ann. hum. Genet.*, **23**, 382-394

Weinstein, E. D. (1965) *Pediatrics*, **35**, 715-718

Woolf, C. M., Woolf, R. M. & Broadbent, T. R. (1963) *Amer. J. hum. Genet.*, **15**, 209-215

Annex 1

CARDS USED FOR RECORDING OF INDIVIDUAL BIRTHS

WHITE CARD FOR SINGLE BIRTHS OR FIRST OF MULTIPLE BIRTHS

WORLD HEALTH ORGANIZATION

COMPARATIVE STUDY OF CONGENITAL MALFORMATIONS

Hospital No.	427642
Hospital	Mother's Name

A	Mother's age in years	8 9
B	Ethnic Group of mother 1 2 3 4 5 6 7	10
C	Number of previous pregnancies	11
D	Consanguinity 1 2 3 4 5 6 7 8 9 0	12
E	Single Birth 1, Twins 2, Triplets 3	13
F	Male 1, Female 2	14
G	Liveborn 1, Stillborn 2	15
H	Malformations: Yes 1, No 2	16
I	If liveborn: Left hospital alive 1, Died in hospital 2	17
J	If stillborn: Autopsy: Yes 1, No 2	18
K	Cause of Death	19 20 21

MALFORMATIONS Describe here and on back of card

No. 3

YELLOW CARD FOR MULTIPLE BIRTHS OTHER THAN THE FIRST

2nd CHILD OF TWINS OR TRIPLETS

Hospital No.................................. Serial No.................................
(*please copy from White Card*)

F	Male 1, Female 2			14
G	Liveborn 1, Stillborn 2			15
H	Malformations: Yes 1, No 2			16
I	If liveborn: Left hospital alive 1, Died in hospital 2			17
J	If stillborn or died: Autopsy: Yes 1, No 2			18
K	Cause of death	19	20	21

MALFORMATIONS DESCRIPTION			
	22	23	24
	25	26	27
	28	29	30
	31	32	33
	34	35	36
	37	38	39

No. 4

Annex 2

BLANK FORMS USED FOR BASIC TABULATIONS BY CENTRES [1]

[1] The complete data recorded on these forms by each centre are given in the Basic Tabulations by Centres booklet, available, upon request, from the Medical Research Council Population Genetics Research Unit, Old Road, Headington, Oxford, England.

WHO/PGRU TABLE Page 1

WORLD HEALTH ORGANIZATION - MALFORMATIONS STUDY

STANDARD TABULATIONS CENTRE ____________

Abbreviations used in tables

M = Male F = Female T = Total LBA = Child left hospital alive LBD = Child died in hospital SB = Stillbirth Y = Yes

N = No NR = Not recorded SNR = Sex not recorded or indeterminate NFS = Not further specified in recording

Malf = Malformation PM = Post mortem or autopsy

TABLE I Summary of outcomes of pregnancies

Pregnancies resulting in	No. of Pregs.	Offspring of pregnancies							
		LBA		LBD		SB		TOTALS	
		Malf	No Malf	Malf	No Malf	Malf	No Malf	Malf	No Malf
Single births									
Twins									
Triplets									
TOTALS									
Grand Totals									

TABLE II Summary of fates of single births by sex

	Malformation				No malformation				Total			
	M	F	NR	T	M	F	NR	T	M	F	NR	T
LBA												
LBD												
Total LB												
SB												
TOTAL BIRTHS												

TWINS

TABLE III Twin types and survival

	M/M Pairs	F/F Pairs	M/F Pairs
Both LBA			
Both LBD			
Both SB			
1 LBA/1 LBD			
1 LBA/1 SB			
1 LBD/1 SB			
TOTAL PAIRS			

TABLE V Malformations by twin types

Malformed	Pair Type	Number of Pairs	Number malformed		
			M	F	T
Neither	MM				
	FF				
	MF				
One	MM				
	FF				
	MF				
Both	MM				
	FF				
	MF				

TABLE IV Malformations. Survival and sex of twins

Malformation	LBA			LBD			SB			TOTAL		
	M	F	T	M	F	T	M	F	T	M	F	T
YES												
NO												
TOTAL												

TABLE VI Triplets and Quadruplets

WHO/PGRU TABLE Page 3

MATERNAL AGES AND PREGNANCY ORDERS - SINGLE BIRTHS

TABLE VII Infants without malformations - single births

Preg-nancy order	Maternal age - years									TOTAL
	0-	15-	20-	25-	30-	35-	40-	45+	NR	
1										
2										
3										
4										
5										
6										
7										
8										
9										
10+										
NR										
Total										

Mean maternal age ______

TABLE VIII Infants with malformations - single births

Preg-nancy order	Maternal age - years									TOTAL
	0-	15-	20-	25-	30-	35-	40-	45+	NR	
1										
2										
3										
4										
5										
6										
7										
8										
9										
10+										
NR										
Total										

Mean maternal age ______

TABLE IX Consanguinity and Ethnic groupings of mothers

Ethnic code	Consanguinity code												%
	1	2	3	4	5	6	7	8	9	0	NR	Total	
1													
2													
3													
4													
5													
6													
7													
8													
9													
0													
NR													
Total													
%													

Ethnic coding

1
2
3
4
5
6
7
8
9
0

Consanguinity coding

1
2
3
4
5
6
7
8
9
0

TABLE Page 5

TABLE X CONSANGUINITY AND SURVIVAL
(SINGLE BIRTHS)

SURVIVAL	CONSANGUINITY CODE											TOTAL
	1	2	3	4	5	6	7	8	9	0	NR	
LBA												
LBD												
SB												
TOTAL												

WHO/PGRU TABLE Page 6

TABLE XI Consanguinity and malformations

Single births

Consan-guinity code	Males		Females		Not recorded		Total	
	Malf	No Malf	Malf	No Malf	Malf	No Malf	Malf	No Malf
1								
2								
3								
4								
5								
6								
7								
8								
9								
0								
NR								
TOTAL								

TABLE XII Ethnic groups and malformations - single births

Ethnic code	Males		Females		Not recorded		Total	
	Malf	No Malf	Malf	No Malf	Malf	No Malf	Malf	No Malf
1								
2								
3								
4								
5								
6								
7								
8								
9								
0								
NR								
TOTAL								

WHO/PGRU TABLE Page 7

TABLE XIII DATA SUMMARY

CENTRE ____________

Single births

Malf
- M ____
- F ____
- NR ____
- T ____

No Malf
- M ____
- F ____
- NR ____
- T ____

All
- M ____
- F ____
- NR ____

Grand Total ____

Single and multiple births

Total Pregnancies ____

Births
- M ____ LBA ____
- F ____ LBD ____
- NR ____ SB ____
- T ____ T ____

Single Births — Mean maternal age
- Malf ____
- No Malf ____

Mean Pregnancy order
- Malf ____
- No Malf ____

Multiple Births

Twin pairs MM ____ FF ____ MF ____
Triplets
Quadruplets

All multiple

Malf
- M ____
- F ____
- NR ____
- T ____

No Malf
- M ____
- F ____
- NR ____
- T ____

All
- M ____
- F ____
- NR ____

Grand Total ____

RATES (Single and multipe births)

Death rate (in hospital) per 1,000 live births ____
Stillbirth rate per 1,000 total births ____
Malformation rate per 1,000 live births ____
Malformation rate per 1,000 still births ____
Malformation rate per 1,000 total births ____
Twinning rate per 1,000 pregnancies ____
Triplet rate per 1,000 pregnancies ____
Malformation rate per 1,000 single pregnancies ____
Malformation rate per 1,000 multiple pregnancies ____

Single births
(Total consanguinity per 1,000 SB and LBD ____
(Total consanguinity per 1,000 LBA ____
(Total consanguinity per 1,000 malformed ____
(Total consanguinity per 1,000 not malformed ____

WHO/PGRU Page 8

TABLE XIV

MINOR DEFECTS CENTRE ______________________

The defects listed below do not appear as malformations in any table. The data relating to the mother and child appear under "Not malformed" in all tables.

Defect	No. of cases			Frequency per 10,000 births
	M	F	T	
Phimosis				
Hypospadias (slight)				
Epispadias (slight)				
Undescended testicles				
Hydrocoele				
Inguinal hernia				
Umbilical hernia (small)				
Minor ear malformations Accessory auricles etc.				
Naevi moles and minor skin blemishes				
Miscellaneous				
TOTAL				

WHO/PGRU Page 9

TABLE XV Frequencies of specific 'major' malformations or groups

SINGLE BIRTHS

CENTRE ____________

Serial code No.	Malformation	Malformed					Consanguinity				Total % Consang.	Ethnic code									
		M	F	NR	T	per 10,000 births	1	2	3	4		1	2	3	4	5	6	7	8	9	0
A	Down's syndrome																				
B 1	Anencephalus																				
2	Anencephalus and S. Bifida																				
3	Hydrocephalus																				
4	Hydrocephalus and S. Bifida																				
5	Occipital meningo(myelo)coele																				
6	"S. Bifida"																				
7	Other neural tube																				
C	Other CNS																				
D	Heart and great vessels																				
E 1	Trach.-oesophag. fist., etc.																				
2	Anal atresia																				
3	Other gastro-intestinal																				
4	Exomphalos																				
F	Diaphragm																				
G 1	Hare lip																				
2	Hare lip and cleft palate																				
3	Cleft palate																				
H	Talipes																				
I	Hip (dislocation or dysplasia)																				

TABLE XV (continued)

Serial code No.	Malformation	Malformed M	Malformed F	Malformed NR	Malformed T	Malformed per 10,000 births	Consanguinity 1	Consanguinity 2	Consanguinity 3	Consanguinity 4	Total % Consang.	Ethnic code 1	Ethnic code 2	Ethnic code 3	Ethnic code 4	Ethnic code 5	Ethnic code 6	Ethnic code 7	Ethnic code 8	Ethnic code 9	Ethnic code 0
J 1	Polydactyly (ulnar)																				
2	Polydactyly (radial)																				
3	All other polydactyly																				
4	Syndactyly																				
5	Other digital anomalies																				
6	Reduction deformities (limbs)																				
7	Other limb deformities																				
K 1	Other local skeletal																				
2	Chondrodystrophy																				
3	Osteogenesis imperfecta																				
4	Pierre Robin syndrome																				
5	Other general skeletal																				
L	Urogenital																				
M	Miscellaneous (single)																				
N	Multiple																				
	TOTAL																				

Code		1	2	3	4	5	6	7	8	9	0	Total
Consanguinity	No.											
	% Total											100.0
Ethnic Group	No.											
	% Total											100.0

Malfs in single births ______ Malfs in multiple births ______ Total ______

	Single births M	Single births F	Single births NR	Single births T
LBA				
LBD				
SB				
T				

WHO/ PGRU —

LISTED "MAJOR" MALFORMATIONS Centre ____________________

Study Number	Sex M/F	LBA LBD SB	Sing. Twin Trip. Quad	Mat. Age	P. M. Y/N	Consang.	Ethnic Group	Malformation(s)	Group	No.

Annex 3

REMARKS ON THE INTERPRETATION OF THE DATA AND AN EXPLANATION AS TO ALLOCATION OF CASES OF MALFORMATIONS IN THE A-N GROUPS

Those recording malformations in this study were asked to describe the anomalies, and, even if the child was thought to be suffering from a specific syndrome, to set out each malformation found.

Ethnic and consanguinity codings for each country are set out in the Basic Tabulations by Centres booklet. Ethnic classifications have to be different for each country and in a number of centres there was some feeling about the use of any coding on an ethnic or on a religious basis and so such codings were not used. In most other centres, as will be seen, such a high proportion of births were to mothers of one ethnic group that virtually no information is available bearing on the relative frequencies of malformations as a whole or specifically in different groups.

As noted in section 1, elaborate consanguinity codings presented difficulties in many centres where the staff were grossly overworked and/or it was difficult to explain to mothers the questions on consanguinity. It is possible, however, to compare consanguinity in all centres on the simple basis of no consanguinity, a relationship closer than first cousins, first cousins, or some degree of known consanguinity less than that of first cousins.

With the exceptions of other malformations associated with the neural tube defects (B1-B7) and Down's syndrome (A), when two or more malformations are present in the same child they are grouped as N (multiple) so that, for example, if all children with a special defect in common were to be sought they might be found (*a*) under the appropriate coding A-M, (*b*) under N (multiple), (*c*) under A or B1-B7, or (*d*) under the heading of a " syndrome " in K2, K3 or K4 or M.

EXPLANATIONS OF THE ARBITRARY GROUPINGS OF MALFORMATIONS A-N

A Down's syndrome: it is clear that Down's syndrome is by no means always recognized at birth and identification is probably more difficult in some ethnic groups than in others. All cases of the syndrome, whether with or without cardiac or other specific malformations, are included.

B Neural tube defects: all cases are included here even if there are accompanying anomalies in other parts of the body.

B1-B2 Anencephalus: is a clear-cut malformation (although it may well be heterogeneous in respect of the underlying or preceding developmental errors) and could hardly be missed.

B3-B4 Hydrocephalus: when present at or shortly after birth it is usually recognized but, particularly in cases where the head enlargement begins only after birth, it may well be missed, especially in hospitals where the mean stay of mothers is short.

B5-B6 Spina bifida and occipital meningocoele: will usually be recognized, although a hard-and-fast line between spina bifida and spina bifida occulta cannot be drawn and anterior meningocoeles may not be recognizable except at autopsy.

B7 Other neural tube: consists mostly of encephalocoele although " cyclops " is included. This is a difficult decision to defend as cyclops may result primarily from failure of development of the facial fronto-nasal process.

C Other malformations of the central nervous system: are not often recorded. They here include microcephaly and other localized malformations usually discovered only at autopsy, e.g., absent corpus callosum. Others are usually associated with another obvious defect, e.g., duplication of the spinal cord in a meningomyelocoele.

D Malformations of the heart and great vessels: are often not detected at birth, or, even if it is realized or suspected that there is cardiac malformation, its nature often cannot be established in a newborn infant unless it comes to autopsy. All cases are included in D *unless* there are other malformations, when they may be in A, B1-B7 or N (multiple).

E1 Tracheo-oesophageal fistula, etc.: this includes oesophageal stenosis, tracheal stenosis and fistula between the viscera with or without stenosis. Most major degrees are probably recognized during the first few days of life although the precise pathology may not be definable except at operation or autopsy. Some cases will be found in N.

E2 Anal atresia: it is not possible from the descriptions given to distinguish in all cases between imperforate anus, anal atresia and stenosis of the rectum. All these are grouped as E2. Any of these, if associated with defects elsewhere (even in the gastrointestinal tract, e.g., tracheo-oesophageal fistula), are grouped as N (multiple).

E3 Most of the defects so grouped are stenosis of gut, but, biliary duct atresia, for example, is also included.

E4 Exomphalos: is used where abdominal contents are protruding into the umbilical cord whether or not there has been rupture. As far as possible small " umbilical hernias " have been excluded and classified as " Minor " but there may be some errors. In one case where the condition was called only " umbilical hernia " on the report card, it was accompanied by a photograph which showed a large exomphalos.

F Defects of the diaphragm: it has not proved possible in all cases to distinguish between hernia of a leaf of the diaphragm, absence of a portion of a leaf of a diaphragm and hiatus hernia. All have been grouped as F and the original description has been followed in the lists of malformations. Associated " aplasia of lung " has been ignored. Some cases are included in N if the associated malformations were not merely the result of contiguity.

G1-G3 Harelip and cleft palate: these three categories are readily recognizable and should be separable, although minimal involvement of the palate may give rise to problems. They have been grouped according to the descriptions given. Those associated with other malformations will be found in N.

H Talipes: presents many problems in nomenclature and there is great variation in opinion as to what should be called talipes and what degree of deformity should be given any treatment or any form of treatment. Many are associated with other malformations and appear in N. In all, the relative frequencies of this condition are more likely to reflect local custom than real frequencies.

I Dysplasia, subluxation and luxation of hip: it seems likely that in some hospitals where all children are tested soon after birth any " clicking " of the hip joint has been recorded as dysplasia of hip. The same remarks on relative frequencies apply as for talipes.

J1-J3 Polydactyly: is relatively common as a sole detectable abnormality. As will be seen from the listings, in many cases no more than " polydactyly " is recorded. In most cases this is probably of the hands and the extra digit is lateral to the fifth finger. In many cases, particularly of ulnar polydactyly, the defect is of no more importance to the individual than many " minor " defects. However, the condition is not usually missed and the geographical and type frequencies are of some interest, so they have been included as " major " malformations. Polydactyly is also commonly associated with other malformations and many consequently appear under N.

J4 Syndactyly: of minor degree in the feet is extremely common and probably often not noticed. The syndactylies shade into the more severes types of deformities of the extremities of the ectrodactyly type and the descriptions recorded seldom make it possible to distinguish between syndactyly and symphalangy.

J5 Other digital deformities: this is a heterogeneous group including the gross disturbances such as ectrodactyly, the varieties of combinations of syndactyly and polydactyly, macrosomia of fingers and toes, etc.

J6 Reduction deformities: have been included as a separate category which includes as extremes absence of one finger or of a whole limb.

J7 Other deformities of limbs: includes such conditions as genu recurvatum and radio-ulnar defects.

K1 Other local skeletal malformations: is used as a separate category to include changes in the spine, ribs, skull, pelvis, etc. It seems likely that many such anomalies are really part of a generalized osseous dystrophy but this would sometimes be demonstrable only by whole-body radiography and so these anomalies are grouped as they have been recorded.

K2-K5 These conditions do not appear to require any explanation. However, whether or not the appropriate combinations of signs are called Pierre Robin syndrome is probably a matter of custom and choice in different hospitals.

L Urogenital: malformations of the urogenital system are seldom single and their precise nature can only be determined at autopsy. A considerable number of " pseudohermaphrodites (NFS) " is included.

M Miscellaneous (single): these malformations are listed and are of great variety. Several traits determined by single-gene mutations, such as albinism, have been included although they do not fit some definitions of congenital malformations.

N Multiple: when there are malformations involving more than one system they have all been specified. In this group ' minor ' malformations have sometimes been included, e.g. deformities of the pinnae of the ear and hypospadias. This is because of their interest as associations and so that the data will be complete for anyone who wishes to make calculations involving the associations of different malformations in the same child.

Minor: These are set out in Table XIV, page 8, in each set of tables in the Basic Tabulations by Centres booklet (see also Annex 2). The decision to call a malformation " Minor " is arbitrary. Many are listed with other malformations in the N group, as mentioned above.

ABBREVIATIONS

An explanation is given in section 2 (page 14), of abbreviations used in the text and tables in this report and in the Basic Tabulations by Centres booklet.